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(Accepted 22 December 2003)

Lesson of the week

Severe cholestatic hepatitis induced by pyritinol

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Severe cholestatic hepatitis may develop in subjects taking pyritinol for minor complaints

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BMJ 2004;328:572–4

Pyritinol is a pyrithioxine derivative marketed in more than 50 countries worldwide. It is approved for "symptomatic treatment of chronically impaired brain function in dementia syndromes" and for "supportive treatment of sequelae of craniocerebral trauma" in various European countries, including Austria, Germany, France, Italy, Portugal, and Greece. In France it is also approved for rheumatoid arthritis as a disease modifying drug, on the basis of the results of clinical trials.[1] It is not licensed for use in the United Kingdom, but in many countries it is available over the counter and is widely advertised on the internet as being for "memory disturbances." From the known sales data, we estimate that more than 100 000 individuals in European Union countries have taken pyritinol in the past five years (assuming a daily dose is 600 mg a day and an average treatment lasts 120 days).

Ascribing severe adverse reactions to drugs such as pyritinol—generally considered innocuous by patients and doctors—is particularly difficult as a link with such drugs is not usually considered. We report on six previously healthy subjects who developed a severe and prolonged form of cholestatic hepatitis during pyritinol treatment and in whom unexpectedly high in vitro CD4+ T cell responses to the drug were documented.

Case reports

Case 1—A 23 year old female student complained of nausea, malaise, and jaundice one month after starting pyritinol 600 mg a day for "memory improvement." She had also been taking paracetamol with codeine sporadically for some years because of headache. Discontinuation of pyritinol led to rapid clinical improvement and to normalisation of liver function five months later.

Case 2—An 18 year old female student was prescribed nitrofurantoin 400 mg a day for cystitis and pyritinol 600 mg a day for "memory improvement." Five days later she was admitted to hospital with pruritus and jaundice of the skin and sclera. One year earlier she had been taking pyritinol at the same dose for 20 days with no known adverse effects. Improvement of her condition was observed after she stopped taking pyritinol, and liver function returned to normal five months later.

Case 3—A 27 year old woman presented at the outpatient clinic with jaundice and abnormal liver function tests. She had been taking oral contraceptives for three years and had started taking pyritinol 400 mg a day 25 days before presenting at the clinic. Liver function returned to normal more than six months after she stopped taking pyritinol.

Case 4—A 21 year old woman was admitted to hospital with malaise, vomiting, and fever of three days' duration and abnormal results for liver function tests. She had been taking pyritinol 600 mg a day for a month and was also taking nimesulide (one or two pills a month) for dysmenorrhoea. After she stopped taking pyritinol, liver function improved but did not return to normal for nine months.

Case 5—Ten days after starting to take pyritinol 600 mg a day, a 41 year old man was admitted to hospital with nausea, vomiting, jaundice, and abnormal liver function. Complete clinical and biochemical normalisation was seen two months after he stopped taking the drug.

Case 6—A 24 year old woman had nausea, vomiting, abdominal pain, fever, and jaundice 14 days after starting to take pyritinol 400 mg a day for "memory improvement." She had also been taking erythromycin 500 mg every six hours during the previous eight days for a sore throat. Liver function returned to normal within a month. When she inadvertently took pyritinol again six months later, she developed the same symptoms and blood tests gave similar results.

Investigations

The table summarises the main features in these six patients, who were referred to our unit in the past 10 years. The pattern of the liver injury was clearly cholestatic, with concentrations of bilirubin exceeding 342 μmol/l in four out of the six patients. The kinetics of the enzymatic changes showed that the highest level of transaminases occurred within the first two weeks, while peaks in alkaline phosphatase and γ-glutamyl transpeptidase were observed two to three months later in most cases. The time taken for normalisation of liver enzymes exceeded three months in four cases, and admission to hospital was required in four. Extrahepatic obstruction of the biliary tree was excluded by liver ultrasonography, and viral hepatitis (A, B, and C) by serology. Liver biopsy was performed in four cases and showed mild inflammatory infiltrate of polymorphonuclear cells, lymphocytes, and sometimes eosinophils with important canalicular and parenchymal cholestasis and mild focal hepatocellular necrosis.

The mechanism for this putative hepatotoxicity of pyritinol is a non-dose dependent one involving metabolic idiosyncrasy or immunological hypersensitivity.[2] To investigate this latter possibility we performed in

Clinical and epidemiological features of the six patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Female	Female	Female	Male	Female
Age (years)	23	18	27	21	41	24
Duration of pyritinol use before first symptoms (days)	28	5	25	34	10	14
Previously used pyritinol (and how long ago)	No	12 months	No	No	Not known	No
Clinical symptoms:						
Nausea or vomiting, or both	Yes	No	Yes	Yes	Yes	Yes
Jaundice	Yes	Yes	Yes	Yes	Yes	Yes
Pruritus	No	Yes	Yes	Yes	Yes	No
Fever	No	No	Yes	Yes	No	Yes
Admitted to hospital	Yes	Yes	No	Yes	Yes	No
Time between stopping pyritinol and normalisation of liver function (days)	157	156	193	270	64	19
Other drugs taken at same time	Paracetamol	Nitrofurantoin	Desogestrel, ethynilestradiol	Nimesulide	None	Piracetam, halazepam, erythromycin
Score on clinical diagnostic scale (positive diagnosis)[8]	14 (probable)	14 (probable)	14 (probable)	12 (possible)	14 (probable)	19 (definite)*
Laboratory features†:						
Aspartate aminotransferase	2	4	16	4	9	5
Alanine aminotransferase	4	12	43	6	20	7
Alkaline phosphatase	4	5	7	12	2	2
γ-glutamyl transpeptidase	11	7	8	22	11	3
Total bilirubin	12	6	10	30	23	5
Pattern of liver injury‡	Cholestatic	Cholestatic	Cholestatic	Cholestatic	Mixed	Cholestatic
Liver ultrasonography	Normal	Normal	Hepatomegaly	Normal	Hepatomegaly	Hepatomegaly
Liver biopsy	Yes	No	Yes	Yes	Yes	No
Autoantibodies	Negative	Mitochondrial	Negative	Negative	Negative	Not done

*Non-intentional positive rechallenge.
†Values are expressed in multiples of the upper limits of normal.
‡Liver injury defined according to the ratio of maximum transaminase to alkaline phosphatase (Council for International Organizations of Medical Sciences).

vitro lymphocyte proliferation assays to the suspected drugs as previously described.[3] Lymphocyte reactivity to pyritinol was shown in all cases investigated (cases 1-5) (fig 1). Maximum stimulation indices were much higher than those previously reported in a large series of patients with drug allergic hepatitis associated with a variety of drugs investigated in our laboratory.[3] Importantly, six healthy controls and three other controls (a female patient who had previously taken pyritinol without adverse effects, a male patient with alcoholic hepatitis with cirrhosis, and a patient with chronic hepatitis B) all showed no lymphocyte responses to pyritinol. In three of our cases, we did sequential studies at 36 months (case 3), 24 and 27 months (case 4), and 3 and 12 months (case 5). A progressive decline in the stimulation index was observed in all cases, although the indices remained clearly above the level considered to be normal (that is, 2). In three cases, we also did proliferation assays to drugs other than pyritinol (nitrofurantoin, erythromycin, and paracetamol with codeine). No reactivity to these drugs was observed either in the patients or the controls.

Figure 2 shows the characterisation of the T cell subsets contributing to the proliferative response, as described in previous work.[4]

Discussion

Although pyritinol has been used in Europe for more than 20 years, only a few cases of drug induced hepatitis have been published.[2 5–7] Interestingly, the doctors who referred the patients to our unit did not consider pyritinol to be a likely cause of hepatitis, so it is possible that this non-dose dependent drug hepatotoxicity may have been substantially under-reported during these years.

These six cases fulfil the usual criteria for diagnosis of drug induced liver injury, namely a temporal relation and the exclusion of alternative causes. Moreover, when we used a semiquantitative diagnostic scale, the results showed high levels of probability for drug induced liver injury.[8] In four patients, immunological investigation showed a marked drug specific in vitro lymphocyte proliferative response, and CD4+ T lymphocytes were identified as the predominant drug specific lymphocytes. What is more striking is that the degree of T lymphocyte reactivity to the drug is much higher than the one usually observed in drug hypersensitivity hepatitis.[3]

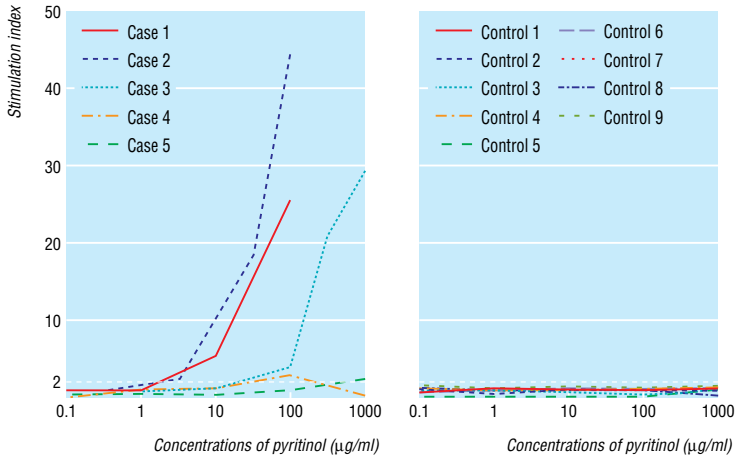

Fig 1 Lymphocyte proliferative responses to pyritinol. Drug stimulation indices in five patients and nine controls assessed by ^{3}H thymidine incorporation after a pulse of 1 microcurie in the previous six hours of the culture and counted in a gaseous scintillation β counter. Values ≤2 are considered to be normal

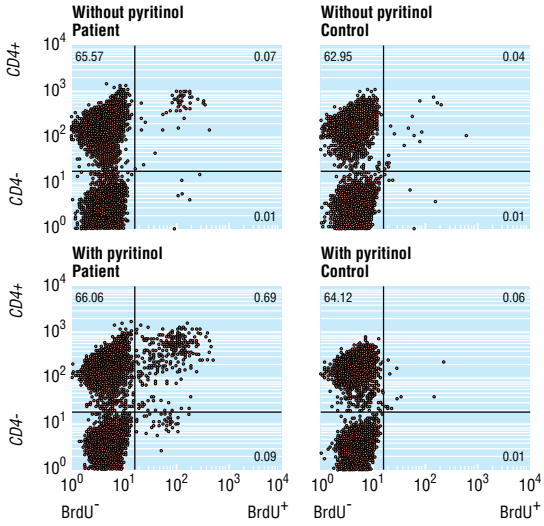

Fig 2 Characterisation of the T cell subsets contributing to the proliferative response in a patient and in a healthy control. Cells were intracellularly stained with antibromodeoxyuridine (BrdU) monoclonal antibody after incubation with BrdU during the previous 24 hours of the culture. Numbers in the upper right quadrant represent the percentage of T cells that are CD4+ and BrdU+ , and those in the lower right quadrant represent the percentage of T cells that are CD4- (CD8+) and BrdU+

Noteworthy, in addition to its putative effect on the memory and intellectual concentration, pyritinol has been shown to have favourable effects on rheumatoid arthritis[1] similar to the ones described for penicillamine, which is also a drug with an active sulfhydryl group.[2] Interestingly, penicillamine is typically responsible for several adverse reactions of immunological nature, such as immune complex nephropathy, autoimmune-like skin disorders, leucopoenia, and thrombocytopoenia.[2]

Clinically, the most striking feature in these patients was the severe and prolonged nature of the cholestasis that required admission to hospital in four previously healthy young individuals. The seriousness of this adverse reaction contrasts with the relatively small clinical importance of the problem that led to its prescription. Therefore, the cases reported here justify a reassessment of the risk and benefit of pyritinol.

Contributors: VM helped in the collection and analysis of clinical data, the performance of immunological studies, the design of the protocol, and the writing of the manuscript. AA helped in the laboratory immunological studies and in writing the manuscript. AL helped in the laboratory immunological studies. AS helped in the design and performance of flow cytometric studies, the analysis of data, and the writing of the mauscript. RV helped to supervise the clinical and laboratory work, plan the study, and write the manuscript. VM will act as guarantor for the article

Funding: The study was in part supported by EU "concerted action" funding: Eurohepatox (European Union BIOMED project PL9 50658).

Competing interests: None declared.

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(Accepted 28 November 2003)

Fluffy thinking

In a hospice setting it is not unusual to be confronted by anguished relatives witnessing the physical deterioration of their loved ones. Their reproachful gaze pierces you and seems to implore you to end their loved ones' suffering. "This is cruel," they so often say, "If this was a pet we would have it put down."

When I was 8 years old I had a pet kitten, Fluffy. He was a funny little black and white bundle of furry joy. He brought us no end of happiness. One day when I came home from school I was not immediately greeted by Fluffy, as was his way. Moments later he appeared, dragging his hind legs. He had been hit by a car and his back was broken. His distress was palpable. He dragged himself home, but he would not allow us too near, fearful of our intentions; he had no flight left, only fight. I can't remember how we managed to get him to the vet's, but the vet simply confirmed what we already knew. He explained that the kindest thing would be to put the cat down. I was inconsolable.

This all happened over 20 years ago. I rarely think about Fluffy, but when I do my memories of his life and death are vivid and still sadden me.

We made the decision to put him down motivated by what we perceived to be his experience of suffering. Was it in his best interests? I would like to think so. Perhaps closer to the truth, but harder to admit to ourselves, was that we knew Fluffy had lost his function as an adorable family pet. Instead of purring and snuggling up to us, he was aggressive, hissing and spitting in spite of our best efforts to help him. He was incontinent and smelly. Mum and Dad had to go to work, I was only 8 years old and a bit scared of him now. Who was going to clean up after him and care for him? On top of all this, he might have needed painkillers and other veterinary input—the bills would have mounted.

I do not believe that our actions were wholly utilitarian, but to say that we acted with pure altruism would be to deceive ourselves. The more I reflect on what we did the more I realise that it was a confused mush of sentiment and pragmatism. But ultimately we did what we did because we could—the option to "put him down" was there.

Truly it would be a brave and terrifying new world if we were able to treat our loved ones as we do our beloved pets.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://submit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.